In the Specification:

After the PCT cover sheet, on page 1, under the title, please amend the following paragraph:

--CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of International Patent Application No. PCT/US00/05547, filed on March 2, 2000, which claims ~~priority to~~ the benefit of U.S. Provisional Patent Application Serial No. 60/122,693, filed on March 3, 1999, the contents of which are incorporated herein by reference in their entirety.—

Please replace the paragraph on page 2, lines 22-25 with the following paragraph:

--In yet another embodiment of the present invention, a method is provided for treating ~~an antifungal~~ a fungal infection in a mammal in need thereof which comprises administering an oral formulation prepared by one of the processes described above to the mammal.--

Please insert the following paragraph as the Abstract after the claims:

--ABSTRACT

--A fluid bed spray process is described where one or more carbohydrates are incorporated into an echinocandin formulation to provide a significant improvement in thermal stability. The carbohydrate is solubilized with an echinocandin compound or echinocandin/carbohydrate complex in a solvent(s) to form a pharmaceutical solution which is sprayed onto the surface of a granular diluent or carrier. The resulting granular oral formulations and medicaments derived therefrom are also described.--

REMARKS/ARGUMENTS

Claims 1-51 were pending in the present application. Claims 22-51 were withdrawn from consideration. Amendment and cancellation of certain claims is not to be construed as a dedication to the public of any of the subject matter of the claims as previously presented. The Applicants expressly reserve the right to file continuation and divisional applications claiming priority to the present application. Amendment of the specification on pages 1 and 2 correct minor typographical errors. An Abstract has been provided as shown in the Amendments to the Specification and on a separate piece of paper attached hereto, as requested by the Examiner. No new matter is believed to have been added.

Regarding the Information Disclosure Statement

The Applicants thank the Examiner for review of the cited references and return of the initialed form PTO-1449.

Rejections under 35 USC §103

Claims 1-21 are rejected under 35 USC §103(a), as allegedly being unpatentable over Lartey et al. (US 5696084) in view of Nielsen-Kahn et al. (US 5972996). The Applicants traverse this rejection.

The Applicants assert that the claimed processes are non-obvious over the above-cited references which neither teach nor suggest the steps of the processes as claimed and do not suggest the surprisingly improved thermal stability, mixability and flowabilty of the granular oral formulations prepared by the claimed process. It appears to the Applicants that, upon review of the reference, the Examiner has made assumptions that are based on hindsight and review of the Applicants' specification rather than the disclosure of the cited references.

The oral pharmaceutical produced by the claimed process is a "granule", that is, a solid. Lartey et al. generically discloses a laundry list of "inert, pharmaceutically acceptable, excipient or carrier[s]" (col. 11, line 42), such as fillers, binders and other substances used in the art of

pharmaceutical formulations for the preparation of solid dosage forms for oral administration (col. 10, lines 39-55). This listing does include sucrose and lactose but does not, generically or specifically disclose "solvents" such as acetone and water, as cited by the Examiner. Further, Lartey et al. does not teach or suggest the preparation of a *solution* or the spraying of that solution. Indeed, with regard to carbohydrates for use in echinocandin solid oral formulations, on column 11, lines 1-4, the reference teaches away from the preparation of a solution and instead teaches that sucrose or lactose be *admixed* with the solid active ingredient (echinocandin). As is known to those of skill in the art, an "admixture" is a mixture of solid substances and does not result in a "solution".

The Examiner admits that the use of a mixture of water and acetone as solvent and other limitations are not taught in the reference (page 3, Office Action). However, the Examiner asserts that Neilson-Kahn et al., teaches that water and acetone are "beneficially advantageous solvent for use with echinocandins". Upon review of Neilson-Kahn et al., the Applicants strongly disagree with this statement. Neilson-Kahn et al. is directed to the synthesis and use of antifungal agents which are derivatives of 4-cyano-4-deformylsordarin. These are *not* in the "echinocandin" class of molecules. The only disclosure pertaining to "echinocandins" appears in col. 16, lines 32-33, in which it is described that the derivatives of 4-cyano-4-deformylsordarin may be used in combination with certain other antifungal compounds, including certain echinocandins. The only disclosures in Neilson-Kahn regarding acetone as solvent appears to the Applicants to be in col. 13, lines 2-45 and col. 24, lines 38-42. In col. 13 is disclosed a 4-cyano-4-deformylsordarin derivative/acetone/triton X155 solution for spaying onto plants (not an oral dosage form, and no use of echinocandin). The disclosure in col. 24 describes the synthesis of "Intermediate 1" as it pertains to synthesis of derivatives of 4-cyano-4-deformylsordarin. The Applicants fail to see how these disclosures are even remotely related to a process for the preparation of a pharmaceutically acceptable solid oral administration dosage form. There appears to be no reason to combine this reference with Lartey et al., and even if one did, the disclosure of either or both of the cited references would not suggest the claimed processes.

Surprisingly, as described throughout the specification (and particularly on page 1, lines 28-29; page 7-page 8 bridging paragraph; page 8, lines 18-21; page 9, lines 9-11; Example 1) the

claimed process results in a granular oral echinocandin formulation which has significantly improved thermal stability. As taught in the specification, a lack of stability of echinocandin compounds (leading to a shelf life in many cases of less than one year at room temperature, page 1, lines 22-23) has heretofor hampered the commercialization of echinocandin oral formulations and their availability for the treatment of fungal infections. As described on page 9, lines 8-11, the claimed process also results in improved mixability and flowability of the granules.

In light of the above remarks, the Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §103 of claims 1-21.

Non-statutory Double Patenting Rejections

A. Claims 1-21 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting, as allegedly being unpatentable over claims of copending commonly owned Application No. US 2002/0160942 (Larew et al.). The Applicants traverse this rejection.

The Applicants fail to see how the *claims* of Larew et al. make obvious the steps of the processes as claimed in the present application. The claims in Larew et al., are directed to the complexes, methods of use and processes for making a complex of carbohydrate and recited echinocandins and result in a crystalline product (see *e.g.,* page 4, lines 21-26 of present application). The claimed complexes and methods of Larew et al., do not teach nor suggest the steps or resulting product of the *processes* claimed in the present application. Indeed, the claimed processes in the present application result in the deposit of a carbohydrate/echinocandin solution *onto* a granular diluent or carrier (*e.g.,* fructose bead) and the present claims can *include* the use of the echinocandin/carbohydrate complex as claimed in Larew et al., as *starting material* for the presently claimed process (*i.e.,* claim 1: "(i) mixing an echinocandin compound or *echinocandin/carbohydrate complex*..."). See, for example page 7, lines 16-21. In other words, the claimed processes result in the deposit of *carbohydrate/echinocandin* solutions onto the granular diluent *or* result in the deposit of *carbohydrate/(echinocandin/carbohydrate complex)* solutions onto the granular diluent.

In light of the above remarks, Applicants respectfully request the withdrawal of the above rejection.

B. Claims 1-21 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting, as allegedly being unpatentable over claims of copending Application No. US 2003/0054981 (Milton et al.). The Applicants traverse this rejection.

The Applicants fail to see how the *claims* of Milton et al. make obvious the steps of the processes as claimed in the present application. The *claims* of Milton et al. are composition claims directed to a *parenteral* echinocandin formulation which incorporates a micelle-forming surfactant. The claims of the present application are directed to processes for the preparation of a solid *oral* dosage formulation. As those of skill in the art are aware, the criteria for effective and palatable solid dosage oral formulations are different from those for effective parenteral formulations. For example, components which enhance stability in the solid oral form may not be suitable or effective if used in a parenteral formulation. Additionally, the *claims* of Milton et al. do not teach nor suggest the steps of the present process claims, particularly the spraying step or the use of a fluidized granular diluent.

In light of the above arguments the Applicants respectfully request the withdrawal of the obviousness-type double patenting rejection.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conversation would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicant(s) petition(s) for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 342312003401. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated September 25, 2003: Respectfully submitted,

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ABSTRACT

A fluid bed spray process is described where one or more carbohydrates are incorporated into an echinocandin formulation to provide a significant improvement in thermal stability. The carbohydrate is solubilized with an echinocandin compound or echinocandin/carbohydrate complex in a solvent(s) to form a pharmaceutical solution which is sprayed onto the surface of a granular diluent or carrier. The resulting granular oral formulations and medicaments derived therefrom are also described.